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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/524,454	03/10/2000	Kristian Berg	697.013US1	5804

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/524,454	BERG ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,8-10 and 24-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,8-10 and 24-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 2, 4, 8-10, 24-29, and newly added Claims 30-34 are pending and being acted being acted upon.

2. Applicant's amendments, remarks, and IDS filed 7/11/07 are acknowledged. In view of Applicant's amendment and response, the previous rejections under the first paragraph of 35 U.S.C. § 112 for inadequate written description of a porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, or tetracycline have been withdrawn. Additionally, the previous rejection under the first paragraph of 35 U.S.C. § 112 for inadequate written description (new matter) has also been withdrawn.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 2, 4, 8-10, 24-29, and newly added Claims 30-34 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could be used for expressing a molecule on a cell, said method comprising photochemical internalization wherein the molecule is sufficient to generate an immune response, for the reasons of record. NOTE: Claims 24-29 were inadvertently left out of the previous rejection due to a typographical error. As those claims also recited a method of stimulating an immune response, it is clear that they were to be included in the rejection. Claim 2 now recites a method of generating a cytotoxic T cell response which is still not enabled by the instant specification.

As set forth previously, the breadth of the claims, in light of the limited disclosure of the specification, would not allow one of skill in the art to practice the invention as broadly claimed without an undue amount of experimentation.

First note that it is clear that the photochemical method (employing certain disclosed agents) of the instant application (and the prior art) can be used to internalize exogenous molecules. The method of the instant claims, however, requires more. The claimed method requires the surface presentation of a sufficient amount of the internalized molecule to generate an immune response.

It is well-known in the immunological arts that only certain antigen presenting cells are capable of presenting antigens and generating an immune response. See, for example, Janeway et al. (1994) wherein it is taught that in addition to antigen presentation, costimulation that can only be provided by B cells, macrophages, or dendritic cells, is required for the generation of an immune response. Accordingly, it appears that the method of Claims 2-5 and 7-11, employing any cell capable of photochemical internalization, could not be performed without an undue amount of experimentation.

Further regarding the breadth of the claims, the specification discloses only the actual use of $AlPcS_{2a}$ and $TPPS_{2a}$ as photochemical internalization agents. Claims 2-7 and 9-11 comprise either no limitations regarding photochemical internalization agents, or as in the case of Claim 7, are drawn to whole classes of agents. The disclosure of two related species of agents cannot be considered to be reasonably sufficient to enable the method of the instant claims to be performed with any of the essentially unlimited number of disclosed families of chemicals without an undue amount of experimentation.

Finally, it remains the Examiner's position that the disclosure of the specification does not sufficiently demonstrate the required limitation that the claimed method be capable of inducing sufficient MHC class I presentation of an antigen to generate an immune response. As set forth previously, the specification fails to disclose any actual Class I MHC presentation. Indeed, the only experiment which might demonstrate any sort of surface presentation, Example 3, clearly demonstrates the opposite, the triangles of Figure 4 show a *lack* of antigen on the surface of the cells.

Applicant's arguments, filed 7/11/07 have been fully considered but they are not persuasive. Applicant argues that Claim 2 no longer requires the generation of "any type of immune response".

The generation of cytotoxic T cell mediated killing is a type of immune response.

Applicant notes that the photosensitizing agents of the claims have been further limited.

Said limiting is noted. The specification still does not show that the agents can generate cytotoxic T cell mediated killing (Claim 2) or an immune response (Claim 24).

Applicant describes the function of MHC I and II.

A review of the specification shows insufficient cell surface presentation of peptides in MHC I or II to generate cytotoxic T cell mediated killing (Claim 2) or an immune response (Claim 24).

Applicant again cites Example 2.

Example 2 was discussed in the Office action of 1/09/07. Regarding Example 2, said example was discussed in the actions of 4/01/05 and 11/29/05:

In regards to Example 2, the methods of the example are not the methods of the instant claims, nor are they representative of the scope of the methods of the instant claims. In the example, a single cell type is loaded with a particular antigen; said loaded cell is then used in a CTL ^{51}Cr release assay. The CTLs employed in a ^{51}Cr assay are primed/activated CTLs and are not representative of the generation or stimulation of an immune response, i.e., the method of the instant claims See, for example, Janeway et al. (1994) wherein one of the fundamental rules of cellular immunology is taught, i.e., that the generation of an immune response from naïve T cells *requires* professional APCs. Clearly then, the ^{51}Cr assay of Example 2 employs primed/activated CTLs and does not comprise the generation or stimulation of an immune response. Note also that the specification discloses that the assay of Example 2 is the assay of Fossum et al. (1995) in which primed CTLs were employed. Accordingly, it remains the Examiner's position that given the breadth of the claimed method, i.e., the employment of *any* cell type in the production of cells capable of generating an immune response (in defiance of one of the fundamental concepts of cellular immunology), the specification provides insufficient support and is not enabling.

Further, because the example comprises no appropriate controls, the skilled artisan would know that no conclusions could be drawn based on the disclosed results. Regarding Claim 6, first note that the limitations of the claim apply only to Claim 6, regardless, neither all types of lymphocytes nor all types of cancer cells are capable of the stimulation/generation of any/all types immune responses as are encompassed by the instant claims.

Also note that the example is not representative of the generation of cytotoxic T cell killing which encompasses the generation of activated T cells from naïve T cells.

Applicant again cites the declaration of Inventor Hogset.

Said declaration was previously considered in the Office action of 2/10/03:

In regards to the 1.132. declaration of Inventor Hogset, it is now disclosed that factors not disclosed in the specification are critical to the functionality of the claimed method. "Whether or not cell death results after photochemical treatment is principally dependent on two factors. Firstly the amount of toxic substances generated by the photosensitizing compounds on exposure to light and secondly, the presence and toxicity of molecules which are internalized during this process." Again, given the lack of guidance in the

specification, the claimed method must then be considered highly unpredictable and requiring of undue experimentation in view of these newly disclosed factors.

Regarding the photosensitizing compounds and exposure to light, while specific photosensitizing compounds are disclosed and claimed, no specific concentrations of said photosensitizing compounds (other than that used in Example 2) are claimed nor disclosed. Clearly, this parameter must be considered in that too much photosensitizing agent will induce cell death. Even more importantly, the declaration discloses that, whereas "the level of toxic substances which are generated may be controlled by the selection of the photosensitizer to be used, [and] the dose of that photosensitizer, but most crucially, the time of illumination which leads to increasing levels of the toxic substances" [must be considered]. The declaration goes on to demonstrate that too little light will not induce internalization while too much light kills the cells. Again it is clear, particularly in regards to the light parameters, i.e., source (wavelength), intensity, and duration, that the specification provides insufficient support for the claimed method. Again, given the lack of guidance in the specification, the claimed method must then be considered highly unpredictable and requiring of undue experimentation.

Finally, regarding the antigen to be internalized, the instant declaration states "the toxicity resulting from the molecules which are introduced may be readily controlled by selecting an appropriate toxic or non-toxic molecule for transfer, depending on the desired end use." The specification discloses however, that essentially any antigen can be used including "all manner" of pathogenic antigens, as well as peptides involved in diseases ranging from cancer to multiple sclerosis. The specification fails, however, to disclose how to "appropriately select" among the toxic and non-toxic molecules. Indeed, even the instant post-filing declaration fails to indicate how such a selection is to be made; it only indicates that said selection is essential, which once again demonstrates the lack of guidance in the specification.

Note that Applicant makes the argument that the Inventor addresses in the declaration how toxicity factors are controlled.

Said addressing of factors critical to the claimed method must be presented in the specification at the time of filing and not in a post-filing declaration.

Applicant argues that Figure 4 is not designed to show the display of antigen.

As such, Example 3 offers little enablement for the claimed method.

As set forth in the Office action of 1/09/07, while most cells express MHC Class I molecules, most cells do *not* express MHC Class II molecules (MHCII is generally expressed only by professional antigen presenting cells, APCs). Second, MHC expression and "antigen display" are not sufficient for the "stimulation of an immune response" (as the term is accepted in the immunological arts) as is required of the viable cell of the claimed method. Indeed, simple display of an antigen, absent the expression of appropriate costimulatory

molecules, would be expected to result in T cell anergy, see Janeway and Travers (1994). Note that the reference further points out that many cancer cells loose even MHCI expression, and thus escape immunological surveillance. Accordingly, only APCs would be enabled for use in the claimed method.

Applicant argues that not all cancer cells lose MHCI expression citing Nijman et al. (2001) and the Examples of the specification.

A review of the reference shows that downregulation of MHCI has indeed been recognized in other instances (page 118, column 1) and that this work was aimed at addressing whether or not downregulation of MHCI was an issue in the ovarian cancers studied by the authors. The fact that it was not an issue in one set of experiments does not negate the fact that it is a recognized phenomena. Regarding the Examples of the specification, MHCI expression (and peptide presentation) sufficient to generate cytotoxic T cell mediated killing (Claim 2) or an immune response (Claim 24) is not shown.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 2, 4, 8-10, 24-29, and newly added Claims 30-34 stand/are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/07432 (IDS). NOTE: Claims 24-29 were inadvertently left out of the previous rejection due to a typographical error. They clearly encompassed the same method as Claims 2, 4, and 8-10 and were intended to be included in the rejection.

As set forth previously, WO96/07432 teaches a method of expressing [now presenting an antigenic molecule on the surface of a viable cancer cell, said method comprising:

contacting said cell *in vitro* [and *ex vivo*] with said antigenic molecule [now peptide] (including a vaccine component, a molecule capable of stimulating an immune response, and a peptide, also including an antigen bound to a carrier molecule) and with a photosensitizing agent (a porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, and tetracycline, including $TPPS_4$, $TPPS_{2a}$, and $AlPcS_{2a}$, also including a photosensitizing agent bound to a carrier molecule), wherein said molecule and said agent are each taken up into an intracellular membrane-restricted compartment of said cell; and irradiating said cell with light of a wavelength effective to

activate the photosensitizing agent, such that the membrane of said intracellular compartment is disrupted, releasing said molecule into the cytosol of the cell, without killing the cell by irradiation, wherein, said released antigenic molecule, or a part thereof of sufficient size to generate an immune response, is subsequently presented on the surface of said cell by a class I MHC molecule (see particularly the claims). Note that reference does not specifically state that the method results in the cell surface expression of the antigen in MHC Class I, however, the reference teaches the same steps as those of the instant claims, thus, said same steps would inherently result in the same outcome, i.e., the claimed method of the expressing an antigenic molecule on the surface of a viable cell.

Applicant's arguments, filed 1/17/06 have been fully considered but they are not persuasive. Applicant argues that the reference does not teach transfer of peptides into the cell, presentation of the peptides on the cell surface, and cytotoxic T cell mediated killing.

The reference teaches the transfer of numerous molecules that can be considered peptides into the cell. See for example Figures 1 and 2. Presentation of the molecules on the cell surface and cytotoxic T cell mediated killing (as well as the generation of an immune response) are properties inherent to the method, i.e. the authors performed the claimed method; said method must result in the outcome of the claimed method.

Applicant cite *Perricone v. Medicus*.

The reversal in *Perricone v. Medicus* was due to a finding that an additional step was employed in the claimed method, i.e., application of lotion to only sunburned skin. Thus, this step of identifying a sunburn before application of the lotion rendered the method patentably distinct. In the instant case both the prior art and the claimed method target cancer cells. Thus, the method of the prior art is the method of the instant claims.

7. The following are new grounds for rejection necessitated by Applicant's amendment.

8. Claim 30 is rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, a method employing a sulfonated tetraphenylporphine, a disulfonated aluminum phthalocyanine or a tetrasulfonated aluminum phthalocyanine.

Applicant cites page 12 of the specification in support for these agents.

A review of the specification fails to show these subgenus's of photosensitizing agents.

9. No claim is allowed.

10. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

12. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR

or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

9/24/07

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